

Mutation-in-Brief

A Novel V2 Vasopressin Receptor Mutation with X-Linked Nephrogenic Diabetes Insipidus

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Congenital nephrogenic diabetes insipidus (NDI) is caused by at least two different genes: the V2 receptor for arginine vasopressin (AVP) in X-linked NDI, and aquaporin-2 (AQP2) in autosomal recessive NDI (1–5). So far, more than 100 mutations have been reported (1, 3, 5, 6). Identification of the mutation of the V2 receptor is useful for early definite diagnosis and an understanding of the pathophysiology of X-linked NDI.

Here we report the identification of a novel insertion mutation of the V2 receptor gene in a patient with X-linked NDI.

Patient Report

A 14-day-old Japanese boy was referred to our hospital because of low grade fever, failure to thrive, and lethargy. He was born after a 38-wk uneventful gestation. His birth weight was 3378 g. The patient was the first child of apparently healthy 25-yr-old parents, although two maternal uncles died in early infancy due to unknown reasons. On admission, his weight was 3672 g. His urine volume was not decreased despite an inadequate fluid intake. Blood test

revealed hyponatremia (158 mEq/L), blood urea nitrogen (20 mg/dl) plasma hyperosmolality (306 mOsm/kg) and urine hypoosmolality (91mOsm/kg). Polyuria continued (2000–3000 ml/m²) and urine specific gravity remained extremely low (1.001–1.002). His plasma ADH was high (38.6 pg/ml, normal range 4–12 pg/ml). An intramuscular injection of 2.5 units did not increase urine osmolality (before 111 mOsm/kg, after 122 mOsm/kg) nor did it change plasma osmolality (before 312 mOsm/kg, after 324 mOsm/kg). Based on these findings, the boy was diagnosed as having congenital NDI. Treatment with hydrochlorothiazide (1 mg/kg/day) was initiated and partial improvement in polyuria (a reduction of 20%) was observed.

The parents of the boy gave their informed consent to participate in the study, and genomic DNA from the patient and his mother was extracted from peripheral leukocytes. The polymerase chain reaction for the V2 receptor gene followed by direct sequencing for the gene was performed according to previous reports (6).

A four base insertion (ins855/856CGCA) was identified in the V2 receptor gene in the patient (Fig. 1a). His mother was shown to be heterozygous for the mutation (Fig. 1b).

Discussion

We identified one novel insertion mutation of the V2 vasopressin receptor gene in a Japanese

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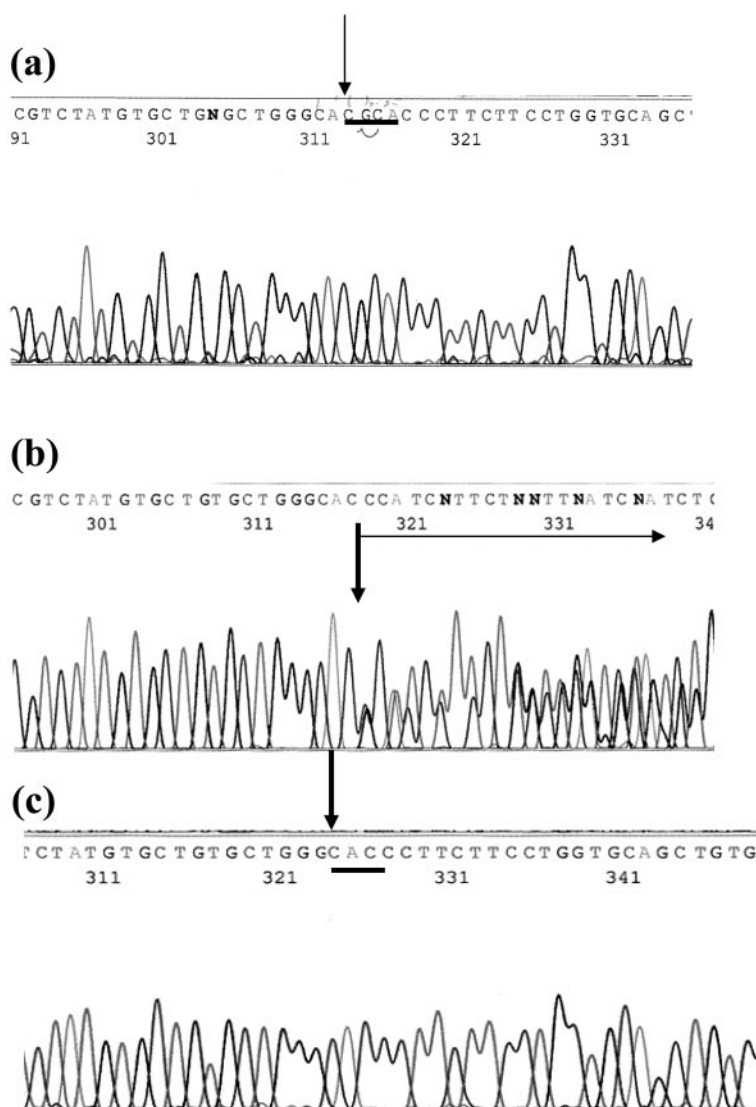


Fig. 1 Sequence analysis of the V2 receptor gene. (a) The patient had a 4 base insertion (855/856insCGCA) denoted by the arrow and underline. (b) His mother had this mutation as a heterozygous state. Note overlapping signals after the insertion site. (c) The sequence of the wild-type gene. The numbers refer to the nucleotides in the genomic sequence in GeneBank accession no L22206; the initial base of the initiation codon is denoted as nucleotides 1.

boy with X-linked NDI. This insertion mutation changes the open reading frame after the mutation site and causes amino acid substitutions in the C-terminal of the V2 receptor. Thus, the

function of the mutant receptor might be impaired.

As mentioned, many mutations have been reported in patients with X-linked NDI. The

mutations are scattered throughout the gene and there is no hot spot in the V2 receptor gene (1–3, 5, 7, 8). Thus, it is required to search for the molecular defect of the V2 receptor gene in each individual.

We did not analyze the patient's grandmother. From family history, her maternal uncles were likely to have been affected and severe dehydration might have been the causes of their deaths in early infancy. This strongly indicates that early diagnosis and adequate therapy are necessary to prevent death and physical and mental retardation in congenital NDI patients (1, 3, 5). For that purpose, molecular diagnosis is a useful method. Not only can the method confirm the diagnosis in suspected individuals, but also in female carriers. Of particular importance is the diagnostic potential of the method in newborn children who are at risk of inheriting this disease.

In conclusion, a new insertion mutation of the V2 receptor gene was identified. We should keep in mind that congenital NDI causes severe sequelae if not diagnosed properly. Molecular diagnosis is useful for early definitive diagnosis and genetic counseling.

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